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Applicants acknowledge that the Office Action was made non-final because the original rejection did not contain the Seki and Cha citations, as Applicants pointed out in a telephonic interview with the Examiner conducted on 07 August 2001. The Examiner was unable to find the correct citations, but upon completion of a new search, identified Seki *et al.* CA 2104649-A (1994) and Cha *et al.* USPN 6,071,693 (Accession Number AR097188).

I. Objections to the Claims

Applicants have amended claim 7 herein to identify the appropriate SEQ ID number (SEQ ID NO:80), as suggested by the Examiner (Office Action, paragraph 3). No new matter has been added by way of this amendment, as support can be found *e.g.*, in Table 1A, page 23.

Claim 34 was objected to under 37 C.F.R. § 1.75(c) as being an improper multiple dependent claim (Office Action, paragraph 4). Claim 34 has been cancelled herein, thereby rendering this rejection moot. New claims 42 and 43 have been added to correct the improper form of cancelled claim 34, and as such, no new matter has been added by way of this amendment. New claim 42 recites a pharmaceutical composition comprising at least two different oligonucleotides according to claim 1 in a pharmacologically acceptable carrier. New claim 43 recites a pharmaceutical composition comprising at least two different oligonucleotides according to claim 2 in a pharmacologically acceptable carrier.

Claims 22-24 and 26 have been found free of the prior art, but are objected to for depending from rejected claims (Office Action, page 7). The rejected claims are addressed in detail below, and Applicants assert that the rejected claims are now in condition for immediate allowance. As such, the objection of these claims is rendered moot.

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Accordingly, Applicants respectfully request that these objections be reconsidered and withdrawn.

II. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 8-21, 25, and 27-31 stand rejected under 35 U.S.C § 112, second paragraph, as allegedly being indefinite (Office Action, paragraph 5). The Examiner opines that it is unclear whether the the claimed oligonucleotides require only one sequence from either of the two recited groups, or require a sequence from both recited groups.

Solely in an effort to advance prosecution of this application, Applicants have amended independent claim 1 to recite a synthetic oligonucleotide complementary to a portion of the 5' untranslated region of hepatitis C virus and having a nucleotide sequence selected from the group consisting of SEQ ID NOS:5, 6, 7, 8, 14, 15, 16, 23, 24, 26, 27, 28, 29, 31, 33, 36, 37, 47, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, and 133, as set forth in Table 1A, Table 1B, and Table 1F.

Applicants submit that independent claim 1, as amended, satisfies the requirements of 35 C.F.R. § 112, second paragraph. Likewise, claims 8-21, 25, and 27-31 (as well as claim 32, and new claims 42 and 43), which are either directly or indirectly dependant on independent claim 1, as amended, and thus contain all the limitations thereof, also satisfy the requirements of 35 C.F.R. § 112, second paragraph.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

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II. Rejection Under 35 U.S.C. § 102.

Claim 1 stands rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Kamada *et al.*, "EP 469342 A2" (Office Action, paragraph 7). Applicants respectfully believe this citation was made in error and that the correct citation should be EP 469348 A2.

Solely in an effort to advance prosecution of this application, Applicants have amended claim 1 to exclude SEQ ID NO:2. Thus, Applicants submit that independent claim 1, as amended, satisfies the requirements of 35 C.F.R. § 102.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

III. Rejection Under 35 U.S.C. § 103

Several rejections under 35 U.S.C. § 103 have been made (Office Action, paragraphs 8-11). In order to respond completely and accurately, Applicants will address each ground separately below.

A. Hogan *et al.* and Maertens *et al.*

Claims 2-6, 8-20, 25, 27, 28, 30, 32 and 33 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hogan *et al.*, USPN 5,424,413 ("Hogan") and Maertens *et al.*, USPN 5,846,704 ("Maertens") (Office Action, paragraph 9).

This ground of rejection is respectfully traversed.

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The Examiner has not rejected independent claim 1 under 35 U.S.C. § 103(a). Thus, Applicants respectfully aver that the Examiner has made the rejection of dependent claim 32, which is directly dependent on claim 1, in error.

Hogan discloses a nucleic acid probe having at least one nucleic acid strand, which has two separate target-specific regions that hybridize to a target nucleic acid, as was suggested by the Examiner. However, the Hogan probes bind contiguous regions on the target nucleic acid, whereas the oligonucleotides encompassed by the instant claims bind at least two non-contiguous regions on the target nucleic acid (see independent claim 2, from which the other rejected claims depend). The Examiner cites Figure 4A in Hogan, to support the contention that these probes render the instant claims obvious. However, as shown in Figure 5A, it is clear that these probes target contiguous regions on the target nucleic acid. Figure 5A is stated to be an "example of the general structure shown in Figure 4" (Hogan, Column 13, line 51). Nowhere does Hogan suggest the use of synthetic oligonucleotides comprising a sequence complementary to at least two non-contiguous regions of an HCV messenger or genomic RNA. The Hogan patent also does not disclose an HCV messenger or genomic RNA, as was acknowledged by the Examiner. Further, Hogan does not teach or suggest the use of synthetic oligonucleotides comprising a sequence complementary to at least two non-contiguous regions of an HCV messenger or genomic DNA

To supply the deficiency in Hogan, the Examiner cites Maertens. The probes in Maertens target contiguous sequences from the 5' untranslated regions of HCV. In contrast, the oligonucleotides encompassed by the instant claims comprise a sequence complementary to at least two non-contiguous regions of HCV messenger or genomic RNA (see independent claim 2,

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from which the other rejected claims depend). Thus, the probes disclosed in Maertens do nothing to supply the deficiency of Hogan. Furthermore, Maertens, either alone or in combination with Hogan, does not teach or suggest the use of synthetic oligonucleotides comprising a sequence complementary to at least two non-contiguous regions of an HCV messenger or genomic DNA.

Thus, Applicants submit that independent claim 2 is non-obvious in view of the teachings of Hogan and Maertens. Similarly, claims 3-6, 8-20, 25, 27, 28, 30 and 33, wherein they depend directly or indirectly upon independent claim 2 (and/or independent claim 1, which was not rejected), and thus contain all the limitations thereof, also satisfy the requirements of 35 U.S.C. § 103(a).

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

B. Hogan et al., Maertens et al., and Seki et al.

Claims 7 and 31 stand rejected under 35 U.S.C. § 103 (a) as allegedly being unpatentable over Hogan, in view of Maertens, and in further view of Seki et al. (CA 2104649) ("Seki") (Office Action, paragraph 10).

This ground of rejection is respectfully traversed.

The Examiner asserts that "[o]ne of ordinary skill in the art would have been motivated to use the probes of [Seki et al.], or obvious variations thereof, in the method as described above because these would have clearly been useful in detecting HCV nucleic acids" (Office Action, paragraph 10 at page 5) (emphasis added). The Examiner further asserts that "[i]t would have

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been prima facie obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods" (Office Action, paragraph 10, at page 5) (emphasis added).

Respectfully, the claims at issue in this rejection encompass oligonucleotides, and do not cover methods, as asserted by the Examiner.

"To establish a *prima facie* case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998); *see also In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (modification of the teachings of a prior art reference is not established by the teachings of a second prior art reference "*unless the prior art suggests the desirability of the modification*" (emphasis added)). Applicants submit that the motivation to combine the cited references is completely lacking.

Hogan and Maertens are discussed in detail elsewhere herein.

With respect to claim 7, the fact that Seki discloses SEQ ID NO:6, which is *partially identical* to SEQ ID NO:47, does not render claim 7 obvious over the combined cited references, does not supply the deficiencies of Hogan and Maertens. Claim 7 is dependent on claim 2, and thus, incorporates all the limitations thereof. Thus, claim 7 requires (1) that the oligonucleotide comprises a sequence complementary to at least two non-contiguous regions of an HCV

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messenger or genomic RNA (see claim 2), and (2) that one portion of the oligonucleotide has the sequence SEQ ID NO:47 (see claim 7). SEQ ID NO:47 is a single sequence, which is specific for only one region of an HCV messenger or genomic RNA. It does not comprise another sequence portion complementary to at least one other non-contiguous region of an HCV messenger or genomic RNA, as required by claim 7, wherein it depends on independent claim 2. Furthermore, Seki does not disclose or suggest an oligonucleotide according claim 2 (which comprises a sequence complementary to at least two non-contiguous regions of an HCV messenger or genomic RNA), wherein one portion of the oligonucleotide has the sequence SEQ ID NO:47. Instead, Seki merely discloses a sequence that may comprise one portion of an oligonucleotide that is complementary to at least two non-contiguous regions of the HCV messenger or genomic RNA.

With respect to claim 31, the fact that Seki discloses SEQ ID NO:229, which is *partially identical* to SEQ ID NO:160, does render claim 31 obvious over the combined cited references, and does not supply the deficiencies of Hogan and Maertens. Claim 31 is dependent on claim 30, which in turn is dependent on claim 8, which in turn is multiply dependent on independent claims 1 or 2. For the reasons set forth above, neither Hogan nor Maertens disclose or suggest a synthetic oligonucleotide comprising a sequence complementary to at least two non-contiguous regions of an HCV messenger or genomic RNA, as is required by independent claim 2. Based on its dependency, claim 31 is not directed solely to an oligonucleotide having the nucleotide sequence of SEQ ID NO:160. Instead, claim 31 is directed to an oligonucleotide having the nucleotide sequence of SEQ ID NO:160, which is modified by incorporating at least one additional triplex forming strand (see claim 30).

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Thus, none of Hogan, Maertens or Seki, either alone or in combination, disclose or suggest the claimed oligonucleotides of claims 7 and 31.

Applicants submit that claims 7 and 31 are non-obvious in view of the combined teachings of Hogan, Maertens, and Seki, and satisfy all the requirements of 35 U.S.C. § 103(a).

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

C. Hogan et al., Maertens et al., and Cha et al.

Claims 21 and 29 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hogan, in view of Maertens, and further in view of Cha *et al.* (U.S. Patent No. 6,071,693) ("Cha") (Office Action, paragraph 11).

This ground of rejection is respectfully traversed.

The Examiner asserts that "[o]ne of ordinary skill in the art at the time of the invention would have been motivated to use probes containing the sequences of the cited references, or obvious variations thereof, in the method discussed above because these would have clearly been useful in detecting HCV nucleic acids" (Office Action, paragraph 11 at page 6) (emphasis added). The Examiner further asserts that "[i]t would have been prima facie obvious to one of ordinary skilled in the art at the time of the invention to carry out the claimed methods" (Office Action, paragraph 11 at page 6) (emphasis added).

Respectfully, the claims at issue in this rejection encompass oligonucleotides, and do not cover methods, as asserted by the Examiner.

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Hogan and Maertens are discussed in detail elsewhere herein.

With respect to claim 21, the fact that Cha discloses SEQ ID NO:126 (see also Accession Number AR097188), which is *partially identical* to SEQ ID NO:122, does not render claim 21 obvious over the combined cited references, and does not supply the deficiencies of Hogan and Maertens. Claim 21 is directed to an oligonucleotide having the nucleotide sequence SEQ ID NO:122, as set forth in Table 1A. Table 1A shows various non-obvious modifications to SEQ ID NO:122. Specifically, Table 1A shows the following sequence: uucgcgaccCAacacuacuc, wherein lower case letters represent 2'-O-methyl ribonucleotides and upper case letters represent deoxyribonucleotides (see footnote in Table 1A, page 25). In contrast, Cha discloses a DNA sequence, which comprises SEQ ID NO:122, but which does not disclose or suggest the modified form SEQ ID NO:122 that is set forth in Table 1A, and which is encompassed by claim 21. Moreover, neither Hogan, Maertens or Cha, either alone or in combination, disclose or suggest such an oligonucleotide.

With respect to claim 29, Applicants respectfully request clarification of this rejection. The Examiner cites SEQ ID NO:39 as being identical to SEQ ID NO:117 of claim 29. The Examiner alleges that SEQ ID NO:39 can be found in the "Seki" reference. However, Applicants have looked at SEQ ID NO:39 in both Seki and Cha and have not found any sequence similarities between Applicants' SEQ ID NO:122 of claim 29 in the instant application, and those referenced sequences. Therefore, clarification is respectfully requested.

However, assuming *arguendo* that a sequence identical to SEQ ID NO:117 were disclosed in the Cha (or Seki) reference, the disclosed sequence would not render claim 29

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obvious. Similar to claim 21 described above, claim 29 is directed to an oligonucleotide having the nucleotide sequence SEQ ID NO:117 (or 118), as set forth in Table 1A. Table 1A shows non-obvious modifications to SEQ ID NO:117. Specifically, Table 1A shows the following modified versions of the sequence: TT*CGCGACCCAACACTACTC (HCV-242), TTCG*CGACCCAACACTACTC (HCV-243), and TT*CG*CGACCCAACACTACTC (HCV-242), wherein *C represents 5-methyl-2'deoxycytidine (see Table 1A, page 24). In contrast, none of the sequences of Cha (and Seki) disclose or suggest the modified form SEQ ID NO:117 that is set forth in Table 1A, which is encompassed by claim 29. Moreover, none of Hogan, Maertens or Cha (or Seki), either alone or in combination, disclose or suggest such an oligonucleotide.

Thus, Applicants submit that claims 21 and 29, are non-obvious in view of the teachings of Hogan, in view of Maertens, and further in view of Cha, and satisfy all the requirements of 35 U.S.C. § 103(a).

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

IV. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully submit that this application is now in condition for immediate allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

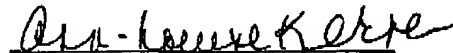
Applicants are submitting this Amendment within three months of the Office Action dated 20 August 2001. Thus, no fees are due in connection with this Amendment. However, if

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there are any other fees due, please charge any underpayment to Deposit Account 08-0219.

Also, please credit any fees underpaid or credit any fees overpaid to the same Deposit Account.

Respectfully submitted,



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